IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Wegert, Sandra L.
David BOTSTEIN, et al.	Art Unit: 1647
Application Serial No. 09/997,628	Confirmation No: 7410
Filed: November 15, 2001	Attorney's Docket No. 39780-2730 P1C30
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on March 30, 2007. A Response was filed July 24, 2007 and an Advisory Action was mailed August 31, 2007. A Notice of Appeal was filed September 26, 2007. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case. A request for a **two month extension of time** is filed concurrently herewith.

The following constitutes the Appellants' Brief on Appeal.

Lee + Song OK

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1097". There exist two related patent applications, (1) U.S. Serial No. 09/997,614, filed November 15, 2001 (containing claims directed to PRO1097 polypeptides), and (2) U.S. Serial No. 09/989,723, filed November 19, 2001 (containing claims directed to nucleic acids encoding PRO1097 polypeptides). These two related applications are also under final rejection from the same Examiner and based upon the same outstanding rejection, therefore appeal of these final rejections are being pursued independently and concurrently herewith.

III. STATUS OF CLAIMS

Claims 1-118 and 124 have been canceled.

Claims 119-123 are in this application.

Claims 119-123 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided in Section VIII.

IV. STATUS OF AMENDMENTS

A summary of the prosecution history for this case is as follows:

Previously, in response to a Final Office Action, an Appeal Brief was filed on August 22, 2005 and an amended Appeal Brief was filed on November 15, 2005. Thereafter, an RCE Response with additional references and affidavits supporting Appellants' arguments was filed July 5, 2006. This Appeal Brief is filed in response to the Final Office Action mailed on March 30, 2007 and the Advisory Action mailed August 31, 2007.

No claim amendments have been submitted after the Final Response of July 24, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to an isolated antibody that specifically binds to the polypeptide of SEQ ID NO: 349 (Independent Claim 119), referred to in the present application as "PRO1097." The invention is further directed to monoclonal antibodies (Claim 120), humanized antibodies (Claim 121), antibody fragments (Claim 122), and labeled antibodies (Claim 123) that specifically bind to the polypeptide of SEQ ID NO: 349. The PRO1097 gene was shown for the first time in the present application to be significantly amplified in human lung or colon cancers as compared to normal, non-cancerous human tissue controls (Example 170).

Support for the preparation and uses of antibodies is found throughout the specification, including, for example, pages 390-395. The preparation of antibodies is described in Example 144, while Example 145 describes the use of the antibodies for purifying the polypeptides to which they bind. Isolated antibodies are defined in the specification at page 315, line 31 (Independent Claim 119). Support for monoclonal antibodies is found in the specification at, for example, page 390, line 17, to page 392, line 3. Support for humanized antibodies is found in the specification at, for example, page 392, line 4, to page 393, line 6. Support for antibody fragments is found in the specification at, for example, page 314, line 30 onwards. Support for labeled antibodies is found in the specification at, for example, page 316, lines 3.

The polypeptide of SEQ ID NO:349 is designated PRO1097, and its amino acid sequence is shown in Figure 244, while the encoding nucleic acid sequence (SEQ ID NO:348) is shown in Figure 243 (Independent Claim 119). The specification discloses that various portions of the PRO1097 polypeptide possess significant sequence similarity to the glycoportease family of proteins and the acyltransferase ChoActase/COT/CPT family (see, for example, page 218, lines 31-34). The isolation of cDNA clones encoding PRO1097 of SEQ ID NO:349 is described in Example 107. Examples 140-143 and page 376, line 12 onwards describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

Finally, Example 170, in the specification at page 539, line 19, to page 555, line 5, sets forth a 'Gene Amplification assay' which shows that the PRO1097 gene is amplified in the genome of certain human lung or colon cancers (see Table 9, page 550). The profiles of various primary lung and colon tumors used for screening the PRO polypeptide compounds of the

invention in the gene amplification assay are summarized on Table 8, page 546 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 119-123 satisfy the utility/ enablement requirement under 35 U.S.C. §101/112, first paragraph.

VII. ARGUMENTS

Summary of the Arguments:

Issue 1: Utility/ Enablement

Appellants submit that patentable utility for the claimed antibodies to PRO1097 polypeptides is based upon the gene amplification data for the gene encoding the PRO1097 polypeptide. The specification discloses that the gene encoding PRO1097 showed significant amplification, ranging from 2.313 to 2.346 fold in two different lung primary tumors and 2.114 to 2.532 fold in three different colon primary tumors. Appellants have submitted, with their Brief filed August 22, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Further, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed September 10, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Second, the Declarations of Dr. Paul Polakis (Polakis I made of record in Appellants' Response filed September 10, 2004, and Polakis II made of record in Appellants' Response filed July 5, 2006), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is good correlation between mRNA levels and polypeptide levels.

In addition, Appellants have filed more than hundred references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, by and large, increased genes/ transcripts levels mostly correlated with increased protein levels, even if accurate predictions of proteins could not be made. The discussions within the Preliminary Amendment filed July 5, 2006, and the arguments therein are hereby incorporated by reference for brevity. While Appellants acknowledge that, in certain instances, DNA/mRNA and protein levels do not correlate, as discussed throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted". In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard".

Appellants submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed September 10, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "**there is a strong correlation between mRNA levels and protein expression**, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, likewise, in the instant application, the Examiner has not presented any evidence specific to the PRO1097 polypeptide to refute Applicant's assertion of a correlation between DNA levels, mRNA levels and protein expression. Appellants add that even though the instant application does not depend on the microarray assay for utility, the facts pertinent to the

Decision on Appeal No. 2006-1469 relate to the instant case as well, because the Decision acknowledges that there is a strong correlation between mRNA levels and protein expression.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the teachings in the art, the Polakis Declarations, the widespread data from the use of array chips, etc., one skilled in the art would agree that in most cases if not all, gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data presented for the PRO1097 gene that the PRO1097 polypeptide is also concomitantly overexpressed. Thus it would follow that the claimed PRO1097 polypeptides have utility in the diagnosis of cancer.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO1097 polypeptides. In addition, one of ordinary skill in the art would also understand how to make and use the claimed antibodies for the diagnosis of lung or colon cancer without any undue experimentation.

Response to Rejections

ISSUE 1. **Claims 119-123 are supported by a credible, specific and substantial asserted utility, and thus meet the utility requirement of 35 U.S.C. § 101/ 112, first paragraph**

The sole basis for the Examiner's rejection of Claims 119-123 under this section is that the data presented in Example 170 of the present specification is allegedly insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. § 101 for the presently claimed subject matter.

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Appellants strongly disagree and, therefore, respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. § 101

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results,

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." [11,12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

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[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. <u>Proper Application of the Legal Standard</u>

Appellants respectfully submit that the data presented in Example 170 starting on page 539 of the specification of the specification and the cumulative evidence of record, which underlies the current dispute, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Example 170 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to <u>quantitatively</u> measure the

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 546). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on page 539, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on . Using this PCR-based assay, Appellants showed that the gene encoding for PRO1097 was amplified, that is, it showed approximately 1.21- 1.23 ΔCt units for lung tumors and 1.08-1.34 ΔCt units for colon tumors which corresponds to $2^{1.21}$ -$2^{1.23}$- fold amplification in lung and $2^{1.08}$ -$2^{1.34}$- fold amplification in colon tumors respectively, or **2.313 to 2.346 fold** in two different lung primary tumors and **2.114 to 2.532 fold** in three different colon primary tumors.

As evidence that the "increase in DNA" in the gene amplification assay is significant, Appellants submitted a Declaration by Dr. Audrey Goddard (with Appeal Brief dated August 22, 2005). The Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.313 to 2.346 fold in two different lung primary tumors and 2.114 to 2.532 fold in three different colon primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further Appellants submit that the fact that two lung tumor samples and three colon tumor samples tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers, which may not give a positive hit with most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO1097 gene is amplified in two lung/ three colon tumors or in most tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO1097 is significant is what lends support to its usefulness as a tumor marker. It was well known in the art at the time of filing of the application that gene amplification, which occurs in most solid tumors like lung and colon cancers, is generally associated with poor prognosis. Therefore, the PRO1097 gene becomes an important diagnostic marker to identify such malignant lung or colon cancers, even if the malignancy associated with PRO1097 molecule is a rare occurrence. Accordingly, the present specification clearly discloses enough evidence that the gene encoding the PRO1097 polypeptide is significantly amplified in certain types of lung or colon tumors and is therefore, a valuable diagnostic marker for identifying certain types of lung or colon cancers.

Yet the Examiner maintains that "the PRO1097 gene has not been associated with tumor formation or development of cancer.....all that the specification does is present evidence that the DNA encoding PRO1097 is amplified in small number of samples" (Page 5 of the Final Office Action dated March 30, 2007). The Examiner once again relies on the teachings of Pennica *et al.* and Hu *et al.*, to allege that, strong opposing evidence exists regarding the prediction of protein expression from corresponding mRNA levels.

Appellants strongly disagree. Appellants submit that the Examiner applied an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellants.

Further, as has been argued throughout prosecution, it is not a legal requirement to establish a "necessary" correlation between an increase in gene copy number and protein expression levels or to find evidence that protein levels can be accurately predicted from gene amplification data. Accordingly, the question is rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation between gene amplification levels and protein levels. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants have already discussed the references Pennica *et al.* and Hu *et al.* in great detail throughout prosecution and in their Response dated January 10, 2007; these discussions and arguments are hereby incorporated by reference. Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. But, the fact that in the case of closely related molecules, there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the

absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general.

Regarding Hu, Appellants respectfully submit that the cited Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO1097 molecule. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different statistical methods*" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature " using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship

established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect *a bias in the literature* to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general.*

Therefore, Appellants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of *one* class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.* or Hu *et al.* by the Examiner.

Appellants also maintain, for the reasons provided in the previously filed responses, that Pennica *et al.*, Haynes *et al.*, Hu *et al.*, Chen *et al.*, Futcher *et al.*, and Gygi *et al.* do not show that a lack of correlation between gene (DNA) amplification and elevated mRNA levels, in general, exists. Appellants' arguments presented in the previously filed Preliminary Amendment of July 5, 2006 are hereby incorporated by reference in their entirety.

For instance, the Examiner cited Chen *et al.* as comparing mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. "twenty-eight of the 165 protein blots(17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found (r= -0.025)."

Appellants submit that the manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship

between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Appellants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not." Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

With respect to Futcher *et al*, the Examiner had asserted that "Futcher *et al.* indicates that 'Gygi *et al.* feel that mRNA abundance is a poor predictor of protein abundance.'"

Appellants respectfully point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient to **accurately** predict the protein level from the level of the corresponding mRNA transcript (see page 1270, Abstract). Contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels. (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies/cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell. (Emphasis added). Therefore, high levels of mRNA **generally**

correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Gygi *et al.* may teach that protein levels cannot be "predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Appellants respectfully submit that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Appellants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

Moreover, Futcher *et al.* point out that the "different conclusions" of Gygi *et al.* are also partly due to different methods of statistical analysis, and to real differences in data. Futcher *et al.* note that Gygi *et al.* used the Pearson product-moment correlation coefficient (r_p) and point out that "a calculation of r_p is inappropriate" because the mRNA and protein abundances are not normally distributed (page 7367, col. 1). In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (r_s), an nonparametric statistic that does not require the data to be normally distributed. Using the r_s, the authors found that mRNA abundance was well correlated with protein abundance ($r_s = 0.74$). Applying this statistical approach to the data of Gygi *et al.* **also** resulted in a good correlation ($r_s = 0.59$), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were normally distributed, in order to allow calculation of an r_p. Two types of transformation (Box-Cox and logarithmic) were used, and **both** resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to

image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo.***" (Page 7367, col. 2; Emphasis added). Thus, while these lowest abundant proteins do show a poor correlation, this is almost certainly due to the less accurate methods used to measure the abundance of these proteins, and **not** to any actual lack of correlation.

The Examiner cited the reference Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 14 of the Final Office Action).

Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (see Evidence list items 5 and 6), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma." (Page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO1097, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold). The PRO1097 gene showed significant amplification of **2.313 fold to 2.346-fold** amplification in lung tumors and **2.114 fold to 2.532-fold** amplification in colon tumors, and thus fully meets this standard. It is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering

gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1097, would be expected to show a corresponding increase in transcript expression.

In conclusion, Appellants have demonstrated a credible, specific and substantial asserted utility for the PRO1097 polypeptides and the antibodies that bind to it, for example, in detecting over-expression or absence of expression of PRO1097. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides and the antibodies that bind to it. Hence, these data clearly support a role of PRO1097 as a lung and colon tumor marker.

Appellants also submit that Example 170 in the specification clearly discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers" (emphasis added). Besides, Appellants have submitted ample evidence (discussed below) to show that, in general, if a gene is amplified in cancer, it is "more likely than not" likely that the encoded protein will also be expressed at an elevated level.

For support, Appellants presented the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed September 10, 2004), who collectively teach that in general, for most genes, DNA amplification increases mRNA expression. The results presented by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary

breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Also, the Declarations of Dr. Paul Polakis (made of record in Appellants' Response filed September 10, 2004 (Polakis I) and July 5, 2006 (Polakis II)), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. For instance, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declarations, show that, in general, there is good correlation between mRNA levels and polypeptide levels.

Appellants further submitted more than 100 references presented in the IDS of July 5, 2006 and maintain that, both Polakis Declarations (Polakis I and II) and the teachings in the art, support Appellants' assertion, in general, that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Appellants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Appellants' asserted utility, a person of skill in the art would conclude that Appellants' asserted utility is "more likely than not true." *Id.*

Moreover, Appellants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging

that "**there is a strong correlation between mRNA levels and protein expression**, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, likewise, in the instant application, the Examiner has not presented any evidence specific to the PRO1097 polypeptide to refute Applicant's assertion of a correlation between DNA levels, mRNA levels and protein expression. Appellants add that even though the instant application does not depend on the microarray assay for utility, the facts pertinent to the Decision on Appeal No. 2006-1469 relate to the instant case as well, because the Decision acknowledges that there is a strong correlation between mRNA levels and protein expression.

Taken together, all of the submitted evidence supports the Appellants' position that, in the majority of amplified genes, increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels, which clearly meets the utility standards described above. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO1097 gene, the PRO1097 polypeptide is concomitantly overexpressed in the lung or colon tumors studied as well.

Appellants further submit that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by an amplified gene in cancer would **still** have a specific, substantial, and credible utility as explained below. As the Declaration of Dr. Avi Ashkenazi (submitted with Appellants' Response filed September 10, 2004) explains:

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Thus, even if over-expression of the gene product does not parallel gene amplification in certain tumor types, parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), submitted with the Response filed September 10, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

In this rejection, the Examiner further relies on the teachings of Bieche *et al.* and Pitti *et al.* to allege that these authors did not use their data for diagnostic purposes, as in the instant application.

Appellants respectfully submit that the references Bieche *et al.* and Pitti *et al.* were first submitted by Appellants in the Goddard Declaration as Exhibits F and G. These references were presented to demonstrate the validity of use of the negative control *i.e.*, the "pooled normal blood controls" as control, which is the control used in the gene amplification assay described in the instant application. The pooled DNA sample control was widely utilized and accepted as a true negative control as demonstrated by use in peer reviewed publications, for instance, in Bieche *et al.* and Pitti *et al.* For example, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; Emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663).

The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control.

However, the Examiner cites these references in the Final Office action to show that Bieche *et al.* and Pitti *et al.* did not use their data for (cancer) diagnostic purposes. Appellants respectfully disagree with the context in which the Examiner makes her interpretation. The fact that Bieche *et al.* and Pitti *et al.* used the pooled blood sample as a negative control in a gene amplification assay is of significance. That Bieche *et al.* and Pitti *et al.* did not use these controls for diagnostic purposes should bear no consequence to the utility for the instant application. Accordingly, the Examiner has not presented valid arguments or contrary evidence to show that the pooled control was not acceptable at the time of filing. Such a rejection is therefore improper.

The Examiner maintains that "the specification provides data purportedly showing a slight increase in DNA copy number in two different types of tumor tissue (lung and colon) of PRO1097" and further alleges that "gene amplification does not reliably correlate with polypeptide over-expression." The Examiner acknowledges that PRO1097 is novel but alleges "it is not known whether PRO1097 is expressed in corresponding normal tissues and what the relative levels of expression are." The Examiner adds that she "cannot find any reason to suspect, that the protein encoded by the PRO1097 gene would confer any selective advantage on a cell expressing it" and that "the instant specification does not teach structure/ function analysis." (Page 3 of the Final Office Action dated March 30, 2007).

Once again, Appellants point out that using the PCR-based assay, Appellants made the assertion that the gene encoding for PRO1097 was significantly amplified. The Declaration by Dr. Audrey Goddard explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample, relative to a normal sample, is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. The Examiner requests "structure/ function data" in the Office Action, but Appellants respectfully remind the Board that this is not a requirement for the utility requirement. Further, the Examiner asks Appellants to show "that the protein encoded by the PRO1097 gene would confer any selective advantage on a cell expressing it." That is, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. Appellants believe that such a requirement is a heightened utility standard imposed by

the Examiner. The mechanism of action need not be understood for attaining that utility. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Thus, Appellants submit that such a concern is misplaced, and cannot properly form the basis of the rejections of the present claims.

Appellants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the antibodies of PRO1097 polypeptide of SEQ ID NO:349 and that the increase in gene amplification for the DNA encoding PRO1097 is sufficient to confer patentable utility to the instantly claimed antibodies to the PRO1097 polypeptides, for the reasons presented throughout the prosecution of this application. Appellants add that the gene amplification data clearly supports a role for PRO1097 and its antibodies as a lung or colon tumor marker.

Thus, based on the asserted utility for PRO1097 in the diagnosis of selected lung or colon tumors, the reduction to practice of the instantly claimed antibodies to the SEQ ID NO: 349 sequence in the present application (also see page 305), the disclosure of a step-by-step protocol for making and expressing PRO1097 in appropriate host cells (in Examples 140-143 and page 376, line 12), the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO1097 protein in the specification (at pages 390-395) and the disclosure of the gene amplification assay in Example 170, the skilled artisan would know exactly how to make and use the claimed antibodies to the PRO1097 polypeptide for the diagnosis of lung or colon cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue'.

Therefore, since the instantly claimed invention is supported by either a credible, specific and substantial asserted utility or a well-established utility, and since the present specification clearly teaches one skilled in the art "how to make and use" the claimed invention without undue

experimentation, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 119-123.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of claims 119-123.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C30**.

Respectfully submitted,

Date: January 28, 2008

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IX. CLAIMS APPENDIX

Claims on Appeal

119. An antibody that specifically binds to the polypeptide of SEQ ID NO: 349.

120. The antibody of Claim 119 which is a monoclonal antibody.

121. The antibody of Claim 119 which is a humanized antibody.

122. The antibody of Claim 119 which is an antibody fragment.

123. The antibody of Claim 119 which is labeled.

X. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

   A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
   B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
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   D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
   E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
   F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
   G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis I).

4. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis II).

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11. Alberts, B., *et al.*, Molecular Biology of the Cell (4rd ed.) In Cell 4th, Figure 6-3 on page 302 Figure 6-90 on page 364 of Cell 4th Cell 4th at 364 Cell 4th at 379.

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Item 1 was submitted with Appellants' Brief filed August 22, 2005.

Items 2, 3 and 98, 5-7 were submitted with Appellants' Response filed September 10, 2004, and were considered by the Examiner as indicated in the Final Office action mailed November 18, 2004.

Items 1(E: Pennica) and item 8 were made of record by the Examiner in the Final Office Action mailed November 18, 2004.

Items 4 and 9-140 were submitted with Appellants' Preliminary Amendment filed July 5, 2006.

Items 141-144 were made of record by the Examiner in the Final Office Action mailed March 30, 2007.

XI. RELATED PROCEEDINGS APPENDIX

None- no decision rendered by a Court or the Board in any related proceedings identified above.